REMARKS

Courtesies extended to Applicants' representatives in the personal interview held on February 24, 2009, are acknowledged with appreciation. The substance of the interview is substantially as set forth in the Examiner Interview Summary dated February 24, 2009, and as set forth herein.

As discussed at the personal interview, in accordance with the present invention, there are provided transdermal patches comprising granisetron loaded into a defined acrylic adhesive, i.e., an acrylic adhesive which is required to contain non-acidic hydroxyl moieties. As demonstrated in the Examples, the combination of adhesive having non-acidic hydroxyl moieties and granisetron provides numerous advantages, e.g.,

-the combination has been found to be remarkably stable;

-the combination has been found to have surprisingly good drug release properties; and

-the combination has been found to have surprisingly good skin flux properties.

That the invention combination of components should provide at least the above-referenced benefits is all the more surprising, given the contrary teaching of prior art such as Effing (WO 98/53815 A1). Indeed, flux and permeation properties of invention patches are so good that it is not necessary to incorporate additives such as skin permeation enhancers in order to achieve desirable performance properties. This is extremely unusual in skin patches. Indeed, the reduction, or even elimination, of additives such as permeation enhancers also means that there is less chance of patches according to the invention causing skin irritation.

Invention patches are suitable for the delivery of granisetron to a subject in need thereof, and find use, for example, in the treatment or prevention of emesis, such as that caused by the administration of chemotherapy to cancer patients.

By the present communication, claims 1 and 34 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as

the amended claim language is fully supported by the specification and original claims. Upon entry of the amendments submitted herewith, claims 1-26 and 28-34 will be pending. The present status of all claims in the application is provided in the Listing of Claims presented herein beginning on page 2 of this communication.

Rejections under 35 U.S.C. § 112

Enablement

The rejection of claim 32 under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to "provide enablement for a method for the treatment and/or prophylaxis of a patient having, or susceptible to, a condition selected from [a defined] group," is respectfully traversed. (See page 2 of the Office Action). Specifically, Applicants respectfully disagree with the Examiner's assertion that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." (See page 3 of the Office Action). Contrary to the Examiner's assertion, one skilled in the art has been provided with more than enough information to use the present invention commensurate in scope with the claims. As readily recognized by one of skill in the art, each of the indications contemplated for treatment by the method of claim 32 have all been demonstrated to be dependent on the 5-HT3 receptor. Taken together with the fact that granisetron, the active component delivered by the adhesive patch of the invention, specifically targets the 5-HT3 receptor (and the showing herein that the adhesive patch of the invention has surprisingly good drug release properties and surprisingly good skin flux properties), one of skill in the art would have every reason to expect the adhesive patch of the invention to be useful for the treatment of each of the indications contemplated by the method of claim 32.

To the extent this rejection relates to the question of whether the specification provides one of skill in the art with sufficient guidance to determine how to use the present invention,

what can be more simple than merely applying an adhesive patch to the skin of a subject in need thereof to provide convenient delivery of the active ingredient?

Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

Written Description

The rejection of claims 1-26 and 28-34 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (See page 5 of the Office Action).

Specifically with respect to claims 1 and 34, and the phrase "at least 6 weeks" as recited therein, it is respectfully submitted that the specification fully supports such language. However, in order to reduce the issues and expedite prosecution, the phrase "at least" has been deleted from these claims. The remaining language, which contemplates stability for the claimed patch for a defined period (6 weeks) at a defined temperature, is fully supported by the specification (see, for example, page 17 thereof).

With respect to the phrase "0.5 to 20% w/w of a monomer containing non-acidic hydroxyl moieties," Applicants respectfully disagree with the Examiner's assertion that the specification allegedly does not provide support for this language. The Examiner's attention is directed to the paragraph bridging pages 6-7 of the specification, where it is explicitly stated that "The functionality, or hydroxyl, comonomer is preferably present in an amount of from 0.5 to 20% w/w, preferably between 3 and 10% w/w by weight of total monomers."

Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

Indefiniteness

The rejection of claims 1-26 and 28-34 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that "[i]t is not entirely clear if the granisetron is loaded in the "acrylic adhesive" composition in line 4, or the granisetron is loaded in the adhesive patch." (See page 6 of the Office Action). Contrary to the Examiner's assertion, the claim, when read in context, is submitted to be clear since the invention adhesive patch is characterized as being a matrix patch (as opposed to a reservoir patch); a matrix patch, by definition, contains the active ingredient in the adhesive layer. However, in order to reduce the issues and expedite prosecution, claim 1 has been amended to explicitly recite that the granisetron is loaded in the **acrylic** adhesive.

Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph are respectfully requested.

Rejections under 35 U.S.C. § 103(a)

. . . over Effing et al. in view of Miranda et al. and Horn et. al.

The rejection of claims 1-26, 28-31, 33 and 34 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Effing et al. (WO 98/53815 A1), in view of Miranda et al. (US Patent No. 5,656,286) or Horn et al. (US Patent No. 3,269,994) is respectfully traversed. As discussed at the personal interview, Applicants' invention, as defined for example by claim 1, distinguishes over the art at least by requiring an adhesive patch suitable for the transdermal administration of granisetron to a subject in need thereof, said patch comprising:

an acrylic adhesive comprising:

50 to 98% w/w of a primary acrylate monomer, and

0.5 to 20% w/w of a monomer containing non-acidic hydroxyl moieties, and

a physiologically effective amount of granisetron loaded in the acrylic adhesive,

wherein the granisetron content of said patch remains substantially unchanged when stored at 25°C for six weeks.

As further discussed at the personal interview, the combination contemplated by the present claims, i.e., adhesive having non-acidic hydroxyl moieties and granisetron, provides numerous advantages, e.g.,

-the combination has been found to be remarkably stable;

-the combination has been found to have surprisingly good drug release properties; and

-the combination has been found to have surprisingly good skin flux properties.

None of the cited art, taken alone or in combination, discloses or suggests such adhesive patches, much less any of the advantages noted above.

In contrast to that which is required by the present claims, Effing et al. clearly teach against the use of an acrylic adhesive containing non-acidic hydroxyl moieties in combination with tropisetron or granisetron. Thus, to the extent that the Office Action relies on the Effing et al. reference, it is incumbent upon the Examiner to consider the reference as a whole, for all that it teaches, not just that which is convenient for the Examiner's purposes. A fair reading of the reference, when taken as a whole, teaches both the interchangeability of tropisetron and granisetron, and the undesirability of using hydroxy-containing monomers (such as 2-hydroxyethylacrylate (HEA)) in the preparation of an adhesive patch containing tropisetron or granisetron.

Specifically, Effing et al. disclose a transdermal patch comprising an adhesive containing A and B monomers. Although granisetron is mentioned as an alternative, the Effing et al. disclosure focuses entirely on tropisetron. Indeed, the Effing et al. Examples make no mention of granisetron.

As discussed at the personal interview, the unwavering focus of Effing et al. on tropisetron is demonstrated in the Examples and the concomitant effect on the description. Effing et al. Example 7 is the only Example that employs an adhesive having a nucleophilic group, and is shown to lose 10% of its tropisetron content after just 4 weeks storage at room temperature. It is of note that the adhesive employed in Effing et al. Example 7 is the only adhesive employed by Effing et al. that causes reduction in tropisetron content of the resulting patch, tropisetron being stable in all of the other adhesives tested. In direct contrast, in Table 5 of Example 2 of Applicants' disclosure, it is shown that granisetron was not only stable in the preferred (nucleophilic) adhesive at low temperature (5°C), but was stable at room temperature (25°C) for a far longer period of time than was evaluated by Effing et al. (i.e., 6 weeks); indeed, granisetron was observed to be stable for 6 weeks at an elevated temperature of 40°C.

As a result of Effing et al.'s failure to recognize any significant structural and/or functional differences between tropisetron and granisetron, the Effing et al. teaching is directed to adhesive patches containing either tropisetron or granisetron. As previously noted (and as discussed at the personal interview), throughout the Effing et al. disclosure, it is suggested that these two compounds are substantially similar both structurally and functionally (see, for example, page 1, line 23-page 2, line 2 of Effing et al., which suggests the interchangeability of these compounds). Indeed, as previously noted, virtually every reference to active drug in the Effing et al. specification is made in the alternative. There are only two exceptions throughout the Effing et al. specification where tropisetron and granisetron are not mentioned in the same clause, i.e., (1) in the background (at page 2, line 10) where "ondansetron and granisetron" are suggested to be interchangeable); and (2) in the Examples, which deal only with tropisetron; however, based on the consistent indication throughout the Effing et al. specification that

tropisetron and granisetron are substantially interchangeable, there is no reason (absent improper reliance on Applicants' disclosure) why one of skill in the art would expect granisetron to perform any differently than tropisetron.

Moreover, as also discussed at the personal interview, not only do Effing et al. teach the interchangeability of tropisetron and granisetron, the reference also teaches the undesirability of using hydroxy-containing monomers (such as HEA) in the preparation of an adhesive patch containing tropisetron or granisetron. Indeed, the reference clearly teaches away from the use of any hydroxy-containing monomer, such as HEA, in the preparation of an adhesive patch containing tropisetron or granisetron, as evidenced by the numerous admonitions throughout the Effing et al. specification that the B monomer should be free of nucleophilic groups (including hydroxyl moieties; see, for example, page 3, line 24 of the specification; page 3, line 30 – page 4, line 1; page 4, lines 8-9; claim 2, lines 1-2; claim 3; claim 12, lines 1-2; and claim 13). Thus, repeatedly throughout their disclosure, Effing et al. assert that "preferably, the B monomer is free of nucleophilic groups."

Indeed, the numerous admonitions throughout the Effing et al. specification that the B monomer should be free of nucleophilic groups are fully consistent with the results of EXAMPLE 7 (at page 13 of Effing et al.), which indicates that an adhesive prepared with 2-hydroxyethylacrylate (HEA) as monomer B suffered from a decrease in drug content of more than 10% within only four weeks of storage at room temperature. This stands in stark contrast to the remaining examples which evaluate the stability of the active drug in the transdermal patch. See, for example, EXAMPLE 1 and EXAMPLE 2 (both at page 11 of Effing et al.), which indicate that full stability is retained at both 25°C and 40°C for at least four weeks with the adhesive formulations employed therein (which include no hydroxy-containing monomers).

Furthermore, of the numerous examples of B monomers set forth at page 3, lines 11-23 of Effing et al., only one contains a free hydroxyl group (2-hydroxyethylacrylate, HEA). One can question, however, why that compound is even included in the list of allegedly suitable

monomers, since, as noted above, the reference, when read in its entirety, makes it clear that use of such a B monomer is disfavored.

Since all of the experiments conducted by Effing et al. are carried out with tropisetron, Effing et al. make the erroneous assumption that whatever applies to tropisetron applies also to granisetron—and merely extrapolates the results with tropisetron to granisetron. Nowhere is granisetron distinguished in any way from tropisetron, and only tropisetron is exemplified. The catastrophic storage experiment with tropisetron (Effing et al. Example 7) results in a very specific teaching away from the use of adhesives containing nucleophilic groups with either tropisetron or granisetron (see page 3 of the Effing et al. disclosure). This comes immediately after a paragraph replete with examples of numerous exemplary B monomers, only one of which contains a nucleophilic group, which is then promptly taught away from as a result of the highly undesirable result therewith.

In view of Effing et al.'s teachings, one of skill in the art would expect that observations made with respect to tropisetron (the only compound with which Effing et al. conducted experiments) would be equally applicable to granisetron. This clearly teaches against the present invention since Effing et al. make it clear that the only B monomer disclosed therein that contains a free hydroxyl group (2-hydroxyethylacrylate, HEA) is disfavored. Thus, one of skill in the art would have no motivation to use a hydroxy-containing monomer such as HEA in the preparation of an adhesive patch containing either tropisetron or granisetron. Even if such motivation existed, based on the teachings of Effing et al., one of skill in the art would have no expectation of success using tropisetron or granisetron with an adhesive such as the adhesive of Effing et al. Example 7. Accordingly, the results reported herein are both surprising and unexpected in view of the teachings of Effing et al.

It is respectfully submitted that the assertion of the Effing et al. reference against the present claims can only be maintained by engaging in improper hindsight analysis, having benefit of Applicants' disclosure. Indeed, it is only upon engaging in improper hindsight

analysis that the Examiner can advance the argument that Effing et al. in any way suggests doing that which Applicant has done. Such use of Applicants' disclosure is clearly improper. It is, therefore, resepectfully submitted that a fair reading of Effing et al., when taken as a whole, actually teaches against that which only Applicants have demonstrated to be of therapeutic value, i.e., adhesive patches suitable for the transdermal administration of granisetron, wherein the adhesive is an acrylic adhesive containing non-acidic hydroxyl moieties, with a physiologically effective amount of granisetron being loaded in the acrylic adhesive.

Thus, to the extent the Examiner elects to rely on the Effing et al. reference, the reference must be considered as a whole, for all that it teaches, not just that which is convenient for the Examiner's purposes. When read as a whole, the reference not only teaches the interchangeability of tropisetron and granisetron, the reference also teaches the undesirability of using hydroxy-containing monomers such as HEA in the preparation of an adhesive patch containing tropisetron or granisetron.

Further reliance on Miranda et al. and/or Horn et al. is unable to cure the deficiencies of Effing et al. Specifically with respect to Miranda et al., this reference does not add anything new to that which Effing et al. already teaches away from. To the extent that Miranda et al. is relevant at all, the reference seeks to solve a problem that is of no concern in the present case, i.e., stopping crystallization of the active ingredient in a matrix adhesive (e.g., by using PVP). Indeed, the whole thrust of Miranda et al. is teaching that incorporation of PVP prevents crystallization, and that is not an issue in the present case. Indeed, it is quite clearly contemplated in the present specification that crystallization can be advantageous (p. 10, "However, crystallisation readily affords a reservoir of drug, which can dissolve into the patch, whence it can be dispensed to the patient, once the patch has been depleted, at least partially, of the initial levels of granisetron.").

Moreover, while Miranda et al. provide many examples, and multiple pages listing numerous possible drugs—but there is no guidance as to what works best for any particular drug.

To the extent there is any guidance with respect granisetron, the preferred formulation taught for granisetron (claim 62) is the blend of polyisoprene etc, with polyisobutylene and polysiloxane together with a polyacrylate and soluble PVP. There is no indication that use of monomer containing non-acidic hydroxyl moieties would be beneficial in any way, much less imparting improved storage and delivery profiles. Indeed, the teaching of Miranda et al. is incredibly broad; it is not proper to selectively pick and choose from the broad Miranda et al. teaching, having benefit of Applicants' disclosure, without there being a suitable pointer as to what works best for the specific compound, granisetron.

Horn et al. is submitted to be irrelevant to the present claims as the reference does not disclose adhesive patches. Instead, the reference merely relates to pressure sensitive adhesives. There is no mention anywhere that such adhesives would be compatible with any other substances, let alone delivery of a substance, and certainly not as being suitable for the delivery of any drugs, much less the specific drug contemplated herein, granisetron.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Effing et al., in view of Miranda et al. or Horn et al., are respectfully requested.

. . . over Seo et al. in view of Miranda et al. and Horn et. al.

The rejection of claims 1-26 and 28-34 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Seo et al. (WO 00/47208 A1), in view of Miranda et al. or Horn et al. is respectfully traversed. Indeed, Seo et al. is respectfully submitted to be non-analogous art. Whereas the present claims contemplate a matrix patch, Seo et al. contemplate a "reservoir" patch (which those of skill in the art recognize to be significantly different structures).

While Seo et al. make reference to a "matrix" patch, it is clear that Seo et al. do not envisage using "matrix" patches as that term is commonly used in the art. Instead, Seo et al. misleadingly use the term "matrix" to refer to the filler in the reservoir. In the art, a reservoir patch is what Seo et al. refer to as a matrix patch (and a matrix patch (as that term is consistently

used in the art) is referred to as an "adhesive matrix patch"). This is clearly shown by Fig. 3 of Seo et al.:

> Fig. 3 shows an embodiment of the monolithic matrix [reservoir] patch of the present invention, which comprises an impervious protective layer(31), a reservoir layer(35), an adhesive layer(33) and a release strip(34).

See page 10 of Seo et al. (emphasis added). The above-quoted passage clearly demonstrates that Seo et al. does not use "matrix" in the accepted manner recognized in patch technology. The Seo et al. "matrix" contains 20 - 80% organic solvent, 1 - 50% PE and 15 - 80% water. In contrast, the adhesive patches of the present invention require no organic solvent, which can lead to skin irritation.

Further evidence that Seo et al. do not relate to matrix patches as contemplated by the present claims is found at p.9, ll. 2-4, where it is stated that:

> An adhesive matrix patch, another form of patch, may not be suitably employed in the present invention because it can carry only limited amounts of an anti-vomiting agent and a soluble skin penetration enhancer in its adhesive layer."

(Emphasis added).

Further reliance on Miranda and/or Horn is unable to cure the deficiencies of Seo et al. For example, as discussed above, Miranda et al. seeks to solve a problem that is of no concern in the present case, i.e., stopping crystallization of the active ingredient in a matrix adhesive (e.g., by using PVP).

As also discussed above, Horn et al. is irrelevant to the present claims.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Seo et al., in view of Miranda et al. or Horn et al., are respectfully requested.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date March 19, 2009

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